Author’s response to reviews

Title: Understanding Side Effects of Therapy for Myasthenia Gravis and their Impact on Daily Life

Authors:

Elizabeth Bacci (elizabeth.bacci@evidera.com)
Karin Coyne (karin.coyne@evidera.com)
Jiat Ling-Poon (poon_jiat_ling@lilly.com)
Linda Harris (linda.harris@alexion.com)
Audra Boscoe (audra.boscoe@gmail.com)

Version: 1 Date: 16 May 2019

Author’s response to reviews:

May 16, 2019

Re: Manuscript ID NURL-D-19-00085

To Whom It May Concern:

We have revised the manuscript, “Understanding Side Effects of Therapy for Myasthenia Gravis and their Impact on Daily Life,” based on the feedback the reviewers and editorial team have provided. We are grateful for the reviewers’ comments and think the manuscript is greatly strengthened by the requisite changes.

Below are our responses to each of the comments.

Reviewer(s)’ Comments to Author

Reviewer #1

1. Did the authors perform validation analyses (especially reproducibility) regarding the Web-based survey?

   o No validation analyses were performed on the web-based survey, however validation analyses are not standard as part of the group concept mapping approach and the study was not designed to develop a questionnaire of MG side effects and impact. We have added a statement in the limitations section.
2. Table 1 shows Refractory Status Classifications, but I'm not sure about the definition of "refractory":
   - The term “refractory” was quickly defined on page 8, as being “unresponsive to treatment.” We have added that definition to Table 1.

3. Why Refractory group is much more than Non-refractory group? (Tables 6 and 7).
   - The sample size in the refractory groups versus the non-refractory group are larger likely because the disease is often difficult to treat, thus the population of individuals with MG that are refractory to treatment is large. Additionally, because the primary objective was to investigate all forms of MG, a more liberal definition of “refractory.” However, analyses were conducted to indicate that the refractory groups did not different significantly on other sociodemographic and clinical characteristics, except for those noted on page 13 (i.e., disability status and number reporting experiencing MG symptoms with breathing higher in the refractory with IVIg group).

4. Side effects and HRQOL may differ according to kind of treatments, dose of drugs, and severity of MG. Especially, steroids may have a great impact. Could you perform the analyses about the difference concerning Side effects and HRQOL between patients with steroids treatment and those without steroids treatment?
   - We appreciate the reviewer’s suggestion, however the side effects associated with oral corticosteroids are often dose and duration dependent (particularly the more severe side effects). As we do not know either the dose or duration of steroid use, we feel this analysis may be misleading as it could include low and high dose steroids as well as short and longer duration.

5. The authors show that side effects of treatment pose a similar burden to patients in terms of severity and tolerability, regardless of MG treatment refractory status. In these patients, much more treatments may be usually performed. Discussion is required.
   - This has been addressed in the discussion. Notably, given the very small N (n=2) in some of the non-refractory group side effects, it would be unlikely to show significance. Additionally, once treatments are stopped due to side effects, patients are likely to forget the full impact and burden of transient side effects which could explain the lack of differences in the current assessment for refractory patients vs non-refractory patients.

Reviewer #2

1. In Phase 1, fourteen adult generalized MG patients were recruited. Authors should comment how these 14 patients were selected.
The participants in Phase 1 were recruited after being approached in person or over the telephone using a standardized screening script by clinic staff. All participants were patients at the clinic that conducted all recruitment activities and had to meet all established inclusion and exclusion criteria. We have added some additional details in the Phase 1 study design section.

2. Did Phase 2 patients consist of generalized MG only? Were some ocular MG included? Table 3 shows that only 41.7% of the Phase 2 patients received oral corticosteroids. This percentage is rather low in the generalized MG group.

   Yes, patients with ocular MG were allowed to participate, however there were no recruitment goals for type of MG. In Phase 2, 90.1% of participants reported ever experiencing MG symptoms in the eye muscles, and 62.0% reported experiencing these symptoms in the last month.

3. Differences of MG type and duration of illness alters the intensity of treatments. Is there any MG-related demographic data such as accompaniment of thymomas, autoantibodies and duration of illness, postintervention status, etc.

   No, this information was not collected as part of this study. We have added a statement about this in the limitations section.

4. Table 4, there are side effect statements such as "muscle weakness", "double vision", and "fatigue". Why are these considered as side effects and not MG symptoms?

   These side effects statements were provided by participants in the Phase 2 brainstorming exercise, specifically in response to the focus prompt: “Some of the treatments people with MG take have side effects. If you have ever experienced a side effect from your MG treatments, what side effects did you experience and how did that impact your life?” Thus, although these can be considered symptoms, only statements about side effects in the brainstorming session were utilized in the sorting and rating task of Phase 2.

5. In. page 12, lines 5-8, authors describe several conditions as serious side effects (blood clots, aseptic meningitis, sepsis, pneumonia, pleural edema, fluid in the heart, allergic/anaphylactic reactions, or internal bleeding). However, in Table 4, I can only find "blood clots" and "aseptic meningitis" and can't find the rest of them.

   Our apologies, this was an error in the table label. Table 4 has been corrected.